

### REVISED ABSTRACT

A new sequence, hGR 1A<sub>p/e</sub>, has been isolated from human DNA upstream from the previously known 2.7 kbp human GR promoter region. This new sequence was found to contain a new promoter (the 1A GR promoter) and a new untranslated exon sequence (GR exon 1A) for the human glucocorticoid receptor protein (hGR). ~~The hGR 1A<sub>p/e</sub> sequence is approximately 25 kilobase pairs upstream of the hGR coding sequence.~~ Alternative splicing produces three different hGR 1A-containing transcripts, 1A1, 1A2, and 1A3. ~~[GR transcripts containing exons 1A1, 1A2, 1B, and 1C are expressed at various levels in many cancer cells and in the human brain.]~~ Exon 1A3-containing GR transcripts appear to be restricted to blood cell cancers and to the human brain. Glucocorticoid hormone treatment caused an up-regulation of exon 1A3-containing GR transcripts in T-lymphoblast cells, and a down-regulation of exon 1A3-containing transcripts in B-lymphoblast cells. ~~This reaction correlates with the known response of the two cells to glucocorticoid hormone treatment, i.e., B-lymphoblast cells are known to be resistant to glucocorticoid hormone treatment and T-lymphoblast cells are known to be sensitive. Thus the presence of exon 1A3-containing transcripts can be used to detect cancerous blood cells that would be sensitive to glucocorticoid hormone treatment.~~ Additionally, an interferon regulatory factor element (IRF-E) that binds IRF-2 was found in the exon 1A sequence. ~~This regulatory factor appears to contribute significantly to basal transcription rate of 1A GR transcripts. The intraxonic location of this sequence was surprising. A glucocorticoid response element (GRE) was also found intraexonically in the exon 1A sequence. The presence of these two regulatory factors indicates that both interferon and glucocorticoid hormone could be used to increase the level of exon 1A3-containing transcripts in the~~

Express Mail No. EK968023137

cells. There are ~~~1075~~ base pairs of hGR 1A promoter sequence, based upon the absence of these sequences in mRNA. There are ~~~981~~ bp of exon 1A sequence. The portions of the hGR 1A/p/c sequence that function as a eukaryotic promoter and intraxonic regions that increase promoter activity were identified based on reporter gene assays. The Thus detection of exon 1A3-containing transcripts can be used for the diagnosis of patients with blood cell cancers, including T-cell acute lymphoblastic leukemia (ALL) ~~and other glucocorticoid-responsive cancers~~, and to identify patients that would benefit from glucocorticoid hormone treatment.